ARIC Manuscript Proposal #2718

PC Reviewed: 3/8/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The predictive ability of relative and absolute change in cardiac troponins classifying non-ST elevation myocardial infarction in the ARIC Community Surveillance study

b. Abbreviated Title (Length 26 characters): Change in troponins classifying NSTEMI

2. Writing Group:

Writing group members: Sameer Arora, Melissa Caughey, Prashant Kaul, Wayne Rosamond, Patty Chang, Joe Rossi, Michael Hall, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SA__ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Manuscript to be completed within 1 year of proposal approval

4. Rationale: In 2007, The ESC/ACCF/AHA/WHF task force released an expert consensus document redefining MI into 5 types.[1] This was further consolidated with the Third Universal Definition of Myocardial Infarction which was released in 2012.[2] The definition of MI was defined as follows:

Detectable fall or rise of cardiac troponins with at least one value exceeding the 99th percentile marked by the manufacturer.[2] If the biomarker criteria was met, one of the following additional criteria had to be met-

1. Symptoms suggestive of ischemia
2. New/ presumed ST-T wave changes or Left Bundle branch block
3. Development of pathological Q waves in the ECG
4. Intracoronary thrombus noted on angiography or autopsy
5. New wall motion abnormality noted on echocardiography

Although a rise or fall in troponin was required, how much rise or fall should satisfy the biomarker criteria for MI?

The American College of Cardiology Foundation supports the 2012 Universal Definition of MI and classifies non-ST elevation acute coronary syndrome by the following:

1. A troponin value above the 99th percentile of the upper reference level and evidence for a *serial increase or decrease of 20%*, if the initial troponin value is elevated
2. For any troponin values below or close to the 99th percentile, evidence for acute myocardial necrosis is indicated by a change of 3 standard deviations of the variation around the initial value as determined by the individual laboratory
3. Clinical laboratory reports should indicate whether significant changes in cardiac troponin values for the particular assay have occurred.

Although a relative change in troponin has largely been agreed on, some reports suggest an absolute change in troponin may be more predictive of AMI in patients[7]. We propose to examine AMI classification by relative and absolute change in troponin values, using a nationally recognized ARIC Communities Surveillance database of patients hospitalized with suspected AMI.

5. Main Hypothesis/Study Questions:

1. In patients hospitalized with Type I non-ST elevation AMI who present with initial troponin values exceeding the 99th percentile, what relative or absolute change in cardiac troponin ideally classifies AMI with optimum sensitivity (compared to the gold-standard validated classification algorithm used by the ARIC Study)?
2. Among hospitalized patients with suspected AMI later determined not to have AMI, what is the 24-hour relative and absolute change in troponins?
3. How do changes in cardiac troponins impact 28-day, 6 month and 1 year mortality rates?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

This analysis will be based on the ARIC Community Surveillance study sample of patients hospitalized with suspected AMI. The analysis will exclude patients classified with ST-elevation AMI, and those lacking serial troponin values at both the first and second day of hospitalization.

All analyses will be weighted by the sampling fraction and adjusted to account for the stratified sampling design. The predictive ability of various relative and absolute cut-points for delta troponin will be analyzed by likelihood ratios[8], and the sensitivity and specificity of these cut-points will be calculated. Model discrimination of absolute and relative delta troponin will be assessed from the receiver operating characteristics[9] of multivariable logistic regression models, using Youden's index to determine the best balanced cut-points optimizing sensitivity and specificity[10]. Potential covariates to include in multivariable models may include renal function, invasive procedures, and year of hospital admission (due to temporal changes in medical management of AMI that have occurred since 1996).

Limitations: The ARIC Surveillance study consists of real-world data abstracted from hospital medical records. Troponin values were not assessed by a standardized, central laboratory, and will vary by manufacturer assay. Additionally, the time from symptom onset to troponin measurement may not be available for all hospitalizations. Finally, this analysis is limited to hospitalizations occurring after 1996, when troponin assessment for suspected AMI became routine.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __x__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __x__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

____x__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MS#2637: Trends in accuracy of hospital discharge diagnosis codes for acute myocardial infarction in the primary and secondary positions, and relation to mortality and coronary revascularization rates. Wayne Rosamond is a coauthor on both this and the current proposals.

MS#1106: Investigating the effect of the AHA 2003 definition of acute CHD on CHD incidence rates in ARIC community surveillance. Wayne Rosamond is a coauthor on both this and the current proposals

MS#965: Characteristics and Outcome of Troponin Elevation in the Absence of Other Criteria for Myocardial Infarction. Wayne Rosamond is a coauthor on both this and the current proposals.

MS#2153 Trends in incidence of hospitalized STEMI and NSTEMI and CHD mortality among 35- 84 year olds in ARIC Community Surveillance 2005-2010. Wayne Rosamond is a coauthor on both this and the current proposals".

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References:

1. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173-95.
2. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581-98.

3. Amsterdam EA, Wenger NK, Brindis RG et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139-228.
4. Thygesen K, Mair J, Katus H et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010;31:2197-204.
5. Eggers KM, Jaffe AS, Venge P, Lindahl B. Clinical implications of the change of cardiac troponin I levels in patients with acute chest pain - an evaluation with respect to the Universal Definition of Myocardial Infarction. *Clin Chim Acta* 2011;412:91-7.
6. Apple FS, Smith SW, Pearce LA, Murakami MM. Delta changes for optimizing clinical specificity and 60-day risk of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome utilizing the ADVIA Centaur TnI-Ultra assay. *Clin Biochem* 2012;45:711-3.
7. Reichin T, Irfan A, Twerenbold R et al. Utility of Absolute and Relative Changes in Cardiac Tropoinin Concentrations in the Early Diagnosis or Acute Myocardial Infarction. *Circulation* 2011; 124:136-45
8. Deeks J, Altman D. Diagnostic Tests 4: Likelihood Ratios. *BMJ* 2004; 329:168-169
9. DeLong E, DeLong D, Clarke-Pearson D. Comparing the Areas Under Two or More Correlated Reciever Operating Characteristic Curves: A Nonparametric Approach. *Biometrics*. 1988; 44:837-845
10. Youden WJ. Index for Rating Diagnostic Tests. *Cancer*. 1950; 3:32-35